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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants : C. Carling, et al.

Serial No. : 07/992,089 Examiner : R. Henley, III

Filed : December 17, 1992 Group Art Unit : 1205

For : COMBINATION OF A BRONCHODILATOR AND STEROIDAL ANTI-INFLAMMATORY DRUG FOR THE TREATMENT OF RESPIRATORY DISORDERS, AS WELL AS ITS USE AND THE PREPARATION THEREOF

I hereby certify that this paper is being facsimile transmitted to: Commissioner of Patents and Trademarks, Washington, D.C. 20231, on September 12, 1994.

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September 12, 1994
Date of Signature

ATTN: EXAMINER RAYMOND J. HENLEY, III

Facsimile No.: 703-308-4556

DECLARATION UNDER 37 C.F.R. § 1.132

I, Jan William Trofast, Ph.D., declare as follows:

I am Principal Research Scientist in Pharmaceutical and Analytical Research and Development at Astra Draco AB in Lund, Sweden, a subsidiary of AB Astra, the assignee of the above-identified application.

I am a coinventor of the subject matter of the above-identified patent application, and I participated in the August 17, 1994 Examiner interview. I am familiar with the office actions issued during the course of prosecution of this application, as well as the prior art patents of Brattsand, et al. and Murakami, et al. cited against the pending claims. The pharmacological *in vivo* studies set forth below were carried out under my direct supervision.

The tests were performed to determine the effect of a fixed combination of budesonide and formoterol on the inhibition of Sephadex-induced lung inflammation. Sephadex was administered intratracheally to Sprague-Dawley rats together with saline (control), budesonide (5 nmol/kg), formoterol (5 nmol/kg) or budesonide and formoterol (5nmol/kg each) in combination. Six animals were subjected to each experimental regimen. The animals were sacrificed the following day, their lungs excised and the inflammatory process measured as lung weight increase due to edema. The effects of the test substances were determined as per cent inhibition of the Sephadex-induced lung edema with the observed lung weight increase of the control animals as reference. The results are presented in Table I below:

TABLE I

Inhibition of Sephadex-Induced Lung Inflammation in Rats

Compound	Amount Administered (nmol/kg)	% inhibition
1. budesonide	5	3.1
2. formoterol	5	21.0
3. budesonide + formoterol	5 + 5	42.1

The data show that budesonide alone inhibited lung-induced edema by 3% and that formoterol alone gave 21% inhibition. By the criterion of the Wilcoxon rank sum test neither of these values are considered to indicate significant inhibition of the Sephadex-induced lung edema. By comparison, the fixed combination of budesonide and formoterol gave 42.1 % inhibition of edema. This value is not only strikingly greater than the sum of the values observed for the individual drugs, but it represents a significant inhibition by the criterion of the Wilcoxon rank sum test. The data indicate that the budesonide-formoterol combination provides unexpected, synergistic enhancement of the effects of the individual drugs against lung inflammation.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date:

JAN W. TROFAST, Ph.D.